UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 11, 2010

SUBJECT: Evaluation of acute and subchronic neurotoxicity studies for paraquat

PC Code: 061601, 061603

DP Barcode: D375436

Decision No.: NA
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0055342

Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 1910-42-5 (paraquat dichloride salt,)
4685-14-7 (paraquat dication)
40 CFR: NA

MRID Nos.: See References

FROM: Jessica Ryman, Ph.D., D.A.B.T., Toxicologist 5/11/2010
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Received in RIC 5/14/2010

I. CONCLUSIONS

Guideline acute (870.6200a) and subchronic (870.6200b) neurotoxicity studies for paraquat submitted by Syngenta have been evaluated. Both studies have been reviewed and found to be acceptable for regulatory use.

II. BACKGROUND

Recent animal studies in the open scientific literature indicate potential for paraquat to cause neurotoxicity in adults and during development. Presently, the toxicity database for paraquat does not include studies designed to specifically investigate acute, subchronic, or developmental neurotoxicity (D261131, Memorandum from J. Ryman and R. Kent to R. Keigwin, March 11, 2009). When paraquat is next evaluated for adequacy of its toxicity database in Registration Review, special attention will be given to neurotoxicity in light of these studies in the open literature.

The registrant (Syngenta) has initiated a research program to investigate the neurotoxic effects of paraquat in more detail. The guideline acute and subchronic neurotoxicity studies described herein were conducted as part of this research program, and to address neurotoxicity for Registration Review.

III. RESULTS/DISCUSSION

The acute neurotoxicity study with paraquat technical (MRID 47994201) is classified as **acceptable, guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

The subchronic neurotoxicity study (dietary) with paraquat technical (MRID 47994201) is classified as **acceptable,** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

MRID AND DATA SUMMARY TABLE

MRID	Guideline
47994201	870.6200a
47994202	870.6200b

EPA Reviewer: Jessica Ryman, PhD, DABT **Signature:**
Risk Assessment Branch IV, Health Effects Division (7509C) **Date:** 5/11/2010
EPA Secondary Reviewer: Ayaad Assaad, DVM, PhD **Signature:**
Toxicology and Epidemiology Branch, Health Effects Division (7509C) **Date:** 5/11/2010
Template version 02/06

TXR#: 0055342

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [§81-8]; OECD 424.

PC CODE: 061601, 061603 **DP BARCODE:** D375436

TEST MATERIAL (PURITY): Paraquat technical (33.4% paraquat ion, 46.1% paraquat dichloride)

SYNONYMS: Paraquat

CITATION: Brammer, A. Paraquat Technical: Acute Neurotoxicity Study in Rats. Central Toxicology Laboratory, Aderley Park, Macclesfield, Cheshire SK10 4TJ, UK. AR7536-REG. June 8, 2006. MRID 47994201. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419-8300, USA.

EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRID 47994201), groups of fasted 42 day-old Alpk:Ap$_f$SD rats 10/sex/dose were given a single oral dose of paraquat technical (33.4% w/w paraquat ion, 46.1% w/w paraquat dichloride, preparation P47) in deionized water orally (by gavage) at 10 mL/kg at doses of 0, 25, 75, or 250 mg/kg paraquat technical/kg body weight. This corresponded to doses of 0, 8.4, 25.1, and 84 mg/kg paraquat ion. Animals were observed for 14 days after dosing. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10/sex/group one week prior to dose administration, at approximately 2 hours after dose administration on Day 1, and at one week (Day 8) and two weeks (Day 15). At study termination, 5/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, 5/sex/group of control and 250 mg/kg animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No effects of the test chemical were observed in the functional observational battery, or on motor activity and nervous system histopathology.

One 250 mg/kg male dosed with paraquat technical (84 mg/kg paraquat ion) was found dead on Day 5. This male had shown a slightly reduced foot splay reflex on Days 1-4 with piloerection and "sides pinched in" on Day 4. One 250 mg/kg female was killed on Day 4, due to adverse clinical signs of irregular breathing (indicative of respiratory distress), flaccidity, "sides pinched

in", and upward spinal curvature from Days 2-4, and piloerection and ocular discharge on Days 3-4. These deaths were considered treatment-related. All other animals survived to scheduled sacrifice. The death and respiratory distress observed in the high-dose animals are consistent with the known pulmonary toxicity of paraquat.

The LOAEL for neurotoxicity was not observed. The NOAEL is 250 mg/kg paraquat technical (84 mg/kg paraquat ion).

This neurotoxicity study is classified as **acceptable, guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

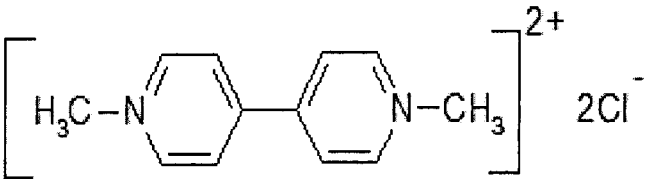
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:

Paraquat

Description: Technical, blue-green liquid, prepared fresh, Expiry./Re-certification date: January 2008
Lot/batch #: P47
Purity: 33.4% (w/w) paraquat ion, 46.1% (w/w) paraquat dichloride
CAS # of TGAI: 1910-42-5 (paraquat dichloride salt,) 4685-14-7 (paraquat dication)
Structure of paraquat dication:



Homogeneity verification not necessary due to true solution; concentration verified quantitatively via HPLC

2. Vehicle and/or positive control: De-ionized water vehicle

3. Test animals:

Species:	Rat	
Strain:	Alpk:ApfSD (Wistar-derived)	
Age/weight at dosing:	At least 42 days old / 259-330 g (males), 189-246 g (females)	
Source:	Rodent Breeding Unit, Alderly Park, Macclesfield, Cheshire, UK	
Housing:	Group housed (3-5 per cage), segregated by sex	
Diet:	CT1 diet (Special Diet Services Limited, Stepfiled, Witham, Essex, UK) *ad libitum* (except overnight prior to dosing)	
Water:	Described as "mains" water, supplied buy an automatic system *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	30-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hrs dark/12hrs light
Acclimation period:	At least 5 days	

B. STUDY DESIGN:

1. In life dates: Start: January 3, 2006 (animals received); End: February 1, 2006 (last FOB, motor activity)

2. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 1. Animals were weighed, randomized by sex, and distributed among treatment groups by a Latin Square, which distributes animals among experimental groups by weight. Unhealthy animals or animals at the extremes of the weight range were excluded. Dose levels were assigned based on a prelimnary neurotoxicity study in this same strain[1]. This report was not submitted to the Agency, and no further details were available. Following an overnight fast, animals were weighed and administered a single dose of deioinized water (vehicle) or paraquat technical in a volume of 10 mL/kg orally by gavage. Ten rats/sex/dose were treated with vehicle

[1]Brammer, A. (2005). Paraquat technical: Acute neurotoxicity study in rats. CTL Report Number CTL/AR7536/REGULATORY/REPORT.

or paraquat technical at 25, 75, or 250 mg/kg (Table 1). It was stated that FOB and motor activity were assessed approximately 2 hours after dosing, but no rationale for the time of peak effect was provided. Animals found dead or killed during the study were examined grossly at necropsy. At terminal sacrifice, 5/sex/dose were anaesthetized in killed by perfusion-fixation with formal saline for neruopathological analysis. The remaining 5/sex/dose were killed by overexposure to halothane and discarded.

TABLE 1. Study design

Experimental parameter	Dose group (mg/kg bw) paraquat technical[1]			
	Control	25	75	250
Total number of animals/sex/group	10	10	10	10
Behavioral testing (FOB, Motor Activity)	10/sex	10/sex	10/sex	10/sex
Neuropathology	5/sex	5/sex	5/sex	5/sex

[1]Dose levels of paraquat ion and paraquat dichloride in paraquat technical were as follows:
25 mg/kg (technical); 8.4 mg/kg (ion), 11.5 mg/kg (dichloride);
75 mg/kg (technical), 25.1 mg/kg (ion), 34.6 mg/kg (dichloride);
250 mg/kg (technical), 84 mg/kg (ion), 115 mg/kg (dichloride)

3. **Test Substance preparation and analysis**: Dosing solutions were freshly prepared on the day of dosing. It was stated that deionized water vehicle was added to a weighed amount of test substance to provide one preparation (w/v) of the required concentration (paraquat technical is in liquid form with paraquat ion and paraquat dichloride expressed as % weight). Homogeneity analysis was not performed because true solutions were formed at all dose levels. Stability analysis was not performed because solutions were prepared fresh. The concentrations of paraquat technical in deionized water for each dose preparation were determined by dilution and detection via HPLC at a limit of detection of 0.03 µg/mL paraquat technical in the analyzed solution (0.03 mg/mL in the formulation concentration). The mean, achieved concentration of paraquat technical in deionized water for each dose preparation were within 6% of nominal concentration and were considered to be satisfactory (Table 2).

TABLE 2. Study design

Experimental parameter	Dose group (mg/kg bw) paraquat technical[1]			
	Control	25	75	250
Nominal concentration (mg/mL)	control	2.5	7.5	25
Analyzed concentration (mg/mL)	ND	2.52/2.49	7.9/7.9	26.6/26.1
Mean concentration (mg/mL)	NA	2.51	7.9	26.4
% of nominal	NA	100.4	105.3	105.6

ND= not detected (limit of detection of 0.03 µg/ml)
NA=not applicable

4. **Statistics:** Males and females were analyzed separately for all measures. Bodyweights were analyzed by ANOVA on separate days. Adjusted mean body weights were determined by correcting for intergroup differences in mean initial bodyweight. These adjusted means were calculated statistically using ANCOVA. Brain weights were also analyzed by ANOVA and adjusted for body weights via ANCOVA. Differences in food consumption, motor activity, time to tail-flick, foot splay, and grip strength were determined by ANOVA. The post-hoc test used to identify where differences were significant from controls was a two-sided student's t-test. Significance was set at $p<0.05$ or $p<0.01$.

C. METHODS / OBSERVATIONS:

1. Mortality and clinical observations: Prior to the start of the study, all rats were examined to ensure that they were physically normal and exhibited normal activity. FOB and motor activity measures were conducted on prior to treatment (Week-1), on Day 1 (approximately 2 hours after dosing), and on Day 8 and Day 15. It was not stated if any other cageside or physical examinations were conducted.

2. Body weight: Animals were weighed on Day -7, Day -1, Day 1 (at approximately 2 hours after dosing), and on Days 8 and 15.

3. Food consumption: Food residues and the amount of food given was recorded continuously throughout the study on a per cage basis at weekly intervals. Food consumption was expressed as a mean value (g food/rat/day) for each cage.

4. Neurobehavioral assessment:

a. **Functional Observational Battery (FOB):** FOB was conducted prior to treatment (Week-1), on Day 1 (approximately 2 hours after dosing), and on Day 8 and Day 15. The observations were made by one, blinded observer and recorded on a computer system by personnel not directly involved in the clinical observations. The presence and/or absence of all listed observations was recorded and the degree of condition noted (slight/moderate/extreme) where appropriate. No information was available on the duration of the observation periods or the kinds of equipment used for quantitative measures.

The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
	Posture*	X	Reactivity*		Mobility
	Biting	X	Lacrimation* / chromodacryorrhea		Rearing+
	Convulsions*	X	Salivation*	X	Arousal/ general activity level*
	Tremors*	X	Piloerection*	X	Convulsions*
X	Abnormal Movements*	X	Fur appearance	X	Tremors*
	Palpebral closure*		Palpebral closure*	X	Abnormal movements*
	Faeces consistency	X	Respiratory rate+	X	Urination / defecation*
X	Vocalization	X	Red/crusty deposits*	X	Grooming (appearance)
	SENSORY OBSERVATIONS	X	Mucous membranes /eye /skin color	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*		Gait score*
X	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behavior*
X	Startle response*	X	Convulsions		Backing
X	Pain response*	X	Vocalization		Time to first step
X	Pupil response*	X	Tremors	X	Vocalization
X	Eyeblink response	X	Ptosis	X	Ataxia
	Forelimb extension	X	Thin appearance/sides pinched in	X	Reduced limb (hind, fore) function
	Hindlimb extension	X	Dehydration	X	Reduced stability
X	Air righting reflex+	X	Urination/defecation	X	Curvature of spine
	Olfactory orientation		**PHYSIOLOGICAL OBSERVATIONS**	X	Piloerection
X	Visual placing response	X	Body weight*	X	Sides pinched in
X	Pinna reflex	X	Body temperature+		**NEUROMUSCULAR OBSERVATIONS**
					Hindlimb extensor strength
			OTHER OBSERVATIONS	X	Forelimb grip strength*
		X	Vocalization during removal from cage	X	Hindlimb grip strength*
		X	Time to tail flick	X	Landing foot splay*
					Rotarod performance
				X	Splay reflex

*Required parameters; +Recommended parameters

b. <u>Locomotor activity</u>: Locomotor activity was evaluated prior to treatment (Week-1), on Day 1 (approximately 2 hours after dosing), and on Day 8 and Day 15. Activity was monitored on an automated activity recording apparatus (Colburn Lab Linc Intra-red Motion Activity System), which records small and large movements as an activity count. Measurements were made on individual animals. Each observation period was divided into 10 scans of 5 minutes in duration in which the animals did not have access to food, water, or items of environmental enrichment. Treatment groups were counter-balanced across test times and devices. Motor activity was assessed in a separate room to avoid disturbances.

<u>5. Sacrifice and pathology:</u> At terminal sacrifice, 5/sex/dose were anaesthetized in killed by perfusion-fixation with formal saline for neruopathological analysis. The remaining 5/sex/dose

were killed by overexposure to halothane and discarded. Tissues taken after perfusion-fixation are summarized below. All tissues from control and high dose group animals were processed for histopathology. Transverse and longitudinal sections of proximal sciatic nerve, proximal tibial nerve, and distal tibial nerve (tibial nerve calf muscle branched) were embedded in resin and semi-thin sections were cut and stained with toluidine blue. All other tissues, including longitudinal sections of spinal cord (at cervical and lumbar swellings) were trimmed and embedded in paraffin wax. Five micron sections were cut and sections were stained with haematoxylin and eosin.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	7 Transverse sections (not specified)		Mid-thigh
	Forebrain		Sciatic Notch
	Center of cerebrum	X	Proximal sciatic nerve*
	Midbrain		
	Cerebellum		**OTHER**
	Pons		Sural Nerve
	Medulla oblongata	X	Tibial Nerve (proximal and distal)*
	SPINAL CORD		Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling	X	Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
	Gasserian Ganglion	X	Cervical dorsal root fibers
	Trigeminal nerves	X	Cervical ventral root fibers
X	Optic nerve*		
X	Eyes (with retina)*		
X	Gastrocnemius muscle*		

6. Positive controls: Positive control studies conducted during 2003-2004 have been reviewed previously. It was concluded from these studies that Central Toxicology Laboratory, UK has demonstrated proficiency in testing for learning and memory with the Y-maze (MRID 46012924), motor activity in pups (MRID 46336201) and adults (MRID 46336203), FOB in adults (MRID 46336203), grip strength in adults (MRID 46336202), and neuropathology and brain morphometry in pups (MRID 46332604) and adults (MRID 46336203).

Additional references listed in the report included MRIDs 43013301, 43013302, 43013304, 43013303, 45811001, 45811002, 45811003, 46012923, and 43013305. These studies were conducted during 1990-2000; it is not known whether they have been reviewed by EPA.

II. RESULTS:

A. OBSERVATIONS:

1. Clinical signs: Treatment-related clinical signs were observed only in animals that were found dead or euthanized for humane reasons as a result of treatment with the test chemical. This was one male and one female dosed with 250 mg/kg paraquat technical. The male was

found dead on Day 5 and had shown a slightly reduced foot splay reflex on Days 1-4 with piloerection and "sides pinched in" on Day 4. The female was killed on Day 4, due to adverse clinical signs of irregular breathing, flaccidity, "sides pinched in", and upward spinal curvature from Days 2-4, and piloerection and ocular discharge on Days 3-4.

2. Mortality: One 250 mg/kg male dosed with paraquat technical (84 mg/kg paraquat ion) was found dead on Day 5. This male had shown a slightly reduced foot splay reflex on Days 1-4 with piloerection and "sides pinched in" on Day 4. One 250 mg/kg female was killed on Day 4, due to adverse clinical signs of irregular breathing, flaccidity, "sides pinched in", and upward spinal curvature from Days 2-4, and piloerection and ocular discharge on Days 3-4. These deaths were considered treatment-related. All other animals survived to scheduled sacrifice.

B. BODY WEIGHT AND BODY WEIGHT GAIN:

There were no significant differences from controls in bodyweights for males and females in any dose group on any day. There were slightly but significantly ($p<0.05$) lower adjusted mean body weights (which corrects for intergroup differences in mean initial bodyweight) of males and females dosed with 250 mg/kg paraquat technical on Day 1 (2 hours post dosing) and remained on Day 8. Also adjusted bodyweights of males in the 75 mg/kg group were statistically lower compared to controls in Day 8 only. However, these differences were small (<5%) and not considered adverse.

C. FOOD CONSUMPTION:

There were no effects of the test substance on food consumption.

D. NEUROBEHAVIORAL RESULTS:

1. FOB findings:

The only FOB finding (besides diarrhea in one 250 mg/kg male on Day 1) was a slight decrease in the foot splay reflex in males and females (Table 7). This reduced reflex was not dose-dependent or consistent. Also, it was not accompanied by changes in foot splay length (data not shown). Therefore, it was not considered adverse.

TABLE 7. Functional observation battery results				
Observation	**Dose level (mg/kg bw)**			
	Control	**25**	**75**	**250**
Males				
Reduced Splay Reflex				
-Week -1	10N	10N	10N	8N/2S
-Day 1 (dosing day)	10N	10N	9N/1S	9N/1S
-Day 8	10N	9N/1S	10N	8N/1S
-Day 15	10N	10N	8N/2S	8N/1S
Females				
Reduced Splay Reflex				
-Week -1	10N	9N/1S	9N/1S	8N/2S
-Day 1 (dosing day)	10N	9N/1S	10N	10N
-Day8	9N/1M	10N	8N/2S	7N/2S
-Day 15	8N/2S	9N/1S	9N/1S	9N/1S

Data were extracted from pages 38 to 65 of the study report.
Values represent incidence where N=absent/normal, S=slight, and M=moderate.

2. **Motor activity**: There were no effects of the test chemical on total motor activity and no consistent or dose-dependent effects of the test chemical on subsession motor activity. Subsessions within all sessions showed habituation.

TABLE 8. Motor activity (total activity counts for session)				
Test day	**Dose level (mg/kg bw)**			
	Control	**25**	**75**	**250**
Males				
Week -1	175.3±50.6 (N=10)	216.8±94.8 (N=10)	242.8±82.1 (N=10)	155.7±70.8 (N=10)
Day 1 (dosing day)	274.6±107.6 (N=10)	310.4±74.9 (N=10)	365.2±110.4 (N=10)	378.8±120.1 (N=10)
Day 8	313.0±153.3 (N=10)	285.1±100.8 (N=10)	299.3±135.5 (N=10)	235.2±89.6 (N=9)
Day 15	387.1±119.4 (N=10)	433.5±118.9 (N=10)	412.8±100.4 (N=10)	344.8±151.9 (N=9)
Females				
Week -1	280.7±106.6 (N=10)	368.0±149.0 (N=10)	382.1±156.0 (N=10)	271.2±104.6 (N=10)
Day 1 (dosing day)	389.1±103.8 (N=10)	320.9±112.6 (N=10)	332.5±152.4 (N=10)	345.8±140.4 (N=10)
Day 8	264.4±136.8 (N=10)	287.3±170.5 (N=10)	318.4±177.3 (N=10)	274.8±79.6 (N=9)
Day 15	345.2±149.8 (N=10)	268.4±107.8 (N=10)	381.0±216.6 (N=10)	364.6±116.3 (N=9)

Data were extracted from pages 74 to 81of the study report.
Values represent mean ±s.d.

E. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** There were no treatment-related gross pathological findings.

2. **Brain weight:**
There were no changes in absolute or relative (to bodyweight) brain weights.

3. **Neuropathology:** There were no treatment-related neuropathological findings. There was demyelination/degeneration in the sciatic and tibial nerves of minimal severity, but it occurred at a similar incidence in both treated and control groups and is a common spontaneous finding. Also, minimal myodegeneration in one 250 mg/kg female was observed, but this is also a common spontaneous finding.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS CONCLUSIONS:

Single oral administration of 250 mg paraquat technical/kg (equivalent to 84 mg paraquat ion/kg) caused adverse clinical signs, consistent with paraquat toxicity (including irregular breathing 2-4 days after dosing) in one female which was killed on Day 4 for humane reasons. Another male at this dose level showed non-specific signs of toxicity on Day 4 and was found dead on Day 5.

Slightly lower body weights were seen 2 hours post dosing on Day 1 in both sexes dosed at 250 mg paraquat technical/kg and on Day 8 in males dosed at 75 and 250 mg paraquat technical/kg, and are considered to reflect general systemic toxicity.

There were no treatment related effects at 25 mg paraquat technical/kg (equivalent to 8 mg paraquat ion/kg).

There was no evidence of neurotoxicity at dose levels up to 250 mg paraquat technical/kg (equivalent to 84 mg paraquat ion/kg).

B. REVIEWER COMMENTS:

This reviewer agrees that this study showed no neurotoxicity in males or females at doses up to 250 mg/kg paraquat technical (84 mg/kg paraquat ion). The only potential neurotoxic sign was a slight decrease in foot splay, but this was slight in severity and sporadic and was not accompanied by changes in foot splay length or histopathology and so was not considered adverse. Another potential neurotoxic sign, piloerection, was accompanied by "sides pinched in" in a 250 mg/kg male found dead on Day 4. The likely explanation for the piloerection is respiratory distress. The cause of death in this animal was not determined, but "sides pinched in" was also observed in a 250 mg/kg female who exhibited irregular breathing, indicative of respiratory distress. This is consistent with the lung being the target organ of paraquat toxicity. Unfortunately, gross and histopathology were limited to the CNS and PNS and the lungs were not examined.

In this particular study, there was clear evidence of systemic toxicity that resulted in the treatment-related deaths of two high-dose animals. The mechanism of paraquat-induced toxicity

(with the exception of neurotoxicity) is well characterized. Paraquat is rapidly absorbed from the small intestine and delivered to multiple organ systems (e.g. liver, heart, kidneys, lungs) where it undergoes redox cycling, causing tissue damage. The kidneys are a major route of elimination of paraquat and so receive high exposure and damage from paraquat cation. However, the lungs are the most susceptible organ system for two reasons. First, there is increased accumulation in the lungs compared to other tissues (due to active transport of paraquat dication). Second, the lungs repair tissue damage from paraquat dication via a fibrotic (scaring) response. This scaring can reduce lung elasticity, resulting in dyspnea, cyanosis, and respiratory failure[1]. The observed effects of death and respiratory distress in a high-dose male and female are consistent with the known respiratory effects of paraquat.

The LOAEL for neurotoxicity was not observed. The NOAEL is 250 mg/kg paraquat technical (84 mg/kg paraquat ion).

C. **STUDY DEFICIENCIES:** No major deficiencies were identified. Palpebral closure was not assessed, however other eye parameters (eye prominence, ptosis) were and were considered sufficient to assess the effects of the test chemical on the eyes.

[1] Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat Poisonings: Mechanisms of Lung Toxicity, Clinical Features, and Treatment. *Critical Reviews in Toxicology,* 38:13–71, 2008

Reviewer: Jessica Ryman, PhD, DABT _____ **Signature:** _____
Risk Assessment Branch IV, Health Effects Division (7509C) **Date:** 5/11/2010
EPA Secondary Reviewer: Ayaad Assaad, DVM, PhD **Signature:** _____
Toxicology and Epidemiology Branch, Health Effects Division (7509C) **Date:** 5/11/2010

TXR#: 0055342

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Neurotoxicity, OPPTS 870.6200b [§82-7]-feeding-rat; (No OECD guideline).

PC CODE: 061601, 061603 **DP BARCODE:** D375436

TEST MATERIAL (PURITY): Paraquat technical (33.4% paraquat ion, 46.1% paraquat dichloride)

SYNONYMS: Paraquat

CITATION: Chivers, S. Paraquat-Subchronic Neurotoxicity Study in the Rat. Central Toxicology Laboratory, Aderley Park, Macclesfield, Cheshire SK10 4TJ, UK. PR1322-REG. June 9, 2006. MRID 47994202. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419-8300, USA.

EXECUTIVE SUMMARY:

In a subchronic neurotoxicity study (MRID 47994202) paraquat technical (33.4% (w/w) paraquat ion, 46.1% (w/w) paraquat dichloride, Batch 216, preparation reference P47) was administered to Alpk:Ap$_f$SD rats 12/sex/group at dose levels of 0, 15, 50, or 150 ppm (equivalent to 0, 1.0/1.1, 3.4/3.9, 10.2/11.9 mg/kg bw/day of paraquat cation in males/females) for 13 weeks. Cageside observations were recorded daily. Detailed clinical observations, including the finding of "no abnormalities detected" were recorded weekly. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10 animals/sex/group one week prior to dosing (pre-test) and in Weeks 1, 4, 8, and 13 of dosing. At study termination, 5/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, 5/sex/dose control and 150 ppm animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no clinical signs associated with the test material, and no effects of the test material were observed in the functional observational battery. There were also no effects of the test material on motor activity. There were also no effects of the test material on brain weights and there were no neuropathological findings.

Dosing was considered adequate, based on a previous studies.

The NOAEL for subchronic neurotoxicity was 150 ppm (equivalent to 10.2-11.9 mg paraquat cation/kg in males/females). The LOAEL was not observed.

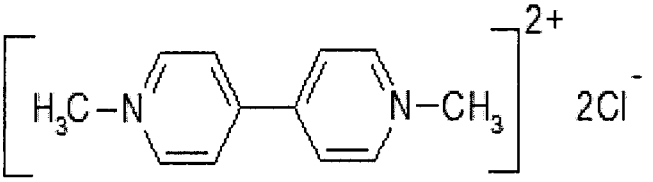
The study is classified as **acceptable, guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Paraquat

Description:	Technical, blue-green liquid, Expiry./Re-certification date: January 2008
Lot/batch #:	Batch 216, preparation reference P47
Purity:	33.4% (w/w) paraquat ion, 46.1% (w/w) paraquat dichloride
CAS # of TGAI:	1910-42-5 (paraquat dichloride salt,) 4685-14-7 (paraquat dication)
Structure of paraquat dication:	

2. Vehicle and/or positive control: Test chemical administered in diet

3. Test animals:

Species:	Rat	
Strain:	Alpk:ApfSD (Wistar-derived)	
Age/weight at dosing:	At least 42 days old	
Source:	AstraZeneca Biological Services, Alderly Park, Macclesfield, Cheshire, UK	
Housing:	Group housed (4-5 per cage)	
Diet:	97% CT1/ 3% RM3 diet (Special Diet Services Limited, Stepfiled, Witham, Essex, UK) *ad libitum*	
Water:	Described as "mains" water, supplied buy an automatic system *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	30-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hrs dark/12hrs light
Acclimation period:	At least 5 days	

B. STUDY DESIGN:

1. In life dates: Start: March 9, 2005; End: September 2, 2005

2. **Animal assignment and treatment:** Animals were assigned to the test groups noted in Table 1. Animals were weighed, randomized by sex, and distributed among treatment groups by a Latin Square, which distributes animals among experimental groups by weight. Unhealthy animals or animals at the extremes of the weight range were excluded.

Dose levels were assigned based on the results of previous studies. In a 28 day dietary study conducted in this same strain at levels of paraquat technical of 100, 150, and 250 ppm, lung pathology and decreased body weight were observed at 250 ppm, but no effects were observed at 150 and 100 ppm[1]. A level of 150 ppm was chosen based on another study[2] in which lung

[1] Chivers, S. (2006). Paraquat: Preliminary study for a 90 day neurotoxicity study in the rat. CTL/KR1594/Technical/Report.

[2] Lindsay,S., Banham, P.B., Goodley, M. *et al.* (1982). Paraquat: multigeneration reproduction study in rats-three generations. ICI CTL/P/719. MRID 00126783.

pathology and toxic signs were noted at 150 ppm but were tolerable, but doses above 150 ppm resulted in severe lung damage that would preclude meaningful evaluation of a subchronic neurotoxicity study. (An EPA review of this same study (MRID 00125783) concluded that 150 ppm produced significant mortality and lung lesions).

Paraquat technical was administered in the diet to 10 rats/sex/dose at dose levels of 0, 15, 50, and 150 ppm of paraquat cation (Table 1) for 90 days. Animals found dead or killed during the study (for humane reasons) were examined grossly at necropsy. At terminal sacrifice, 5/sex/dose were anaesthetized and killed by perfusion-fixation with formal saline for neruopathological analysis. The remaining animals were discarded.

TABLE 1. Study design

Experimental parameter	Dose group of paraquat cation (in ppm)			
	Control	15	50	150
Total number of animals/sex/group	12	12	12	12
Behavioral testing (FOB, Motor activity)	12/sex	12/sex	12/sex	12/sex
Neuropathology	5/sex	5/sex	5/sex	5/sex
Mean dose paraquat cation received (mg/kg/day) M/F	Control	1.0/1.1	3.4/3.9	10.2/11.9
Equivalent in paraquat dichloride (ppm) M/F	Control	1.4/1.5	4.7/5.4	14.1/16.4

3. Test Substance preparation and analysis:

All diets were based on CT1/RM3 (97% CT1 plus 3% RM3). Diets were prepared in 30 kg batches from premixes by grinding paraquat with 1000g milled RM3 diet in a Kenwood Chef for 10 minutes. The premix was added to the CT1 diet to make up to 30 kg and mixed in a Pharma Matrix Blender Model PMA 100S (T K Fielder) for 6 minutes. During preparation, 100 ml of deionized water was used to wash out any residual paraquat from the test vials. Diets were stored at ambient temperature and were prepared monthly (17-March, 11-April, 18-May). Concentration was sampled on the days the diets were prepared. Homogeneity was sampled on 17-March and 18-May. Stability was tested 42 days after diets were prepared on 18-May.

Results

Homogeneity analysis: This was analyzed on two dates: 17-March-05 and 18-May-05 for 15 ppm and 150 ppm samples. On 17-March, there was high variability in the 15 ppm samples (24.7-50.7%) but acceptable variability in the 150 ppm samples (-5.7-5.0%). On 18-May, variability for 15 ppm samples was -4-8.6%, while variability for 150 ppm samples was -7.6-5.1%.

Stability analysis: 2.2% (150 ppm) - 6.2% (15 ppm)

Concentration analysis: 0-1.3% (15 ppm), 2.6-5.4% (50 ppm), 4.7-14.3% (150 ppm)

The analytical data indicate that the mixing procedure was adequate on 18-May for all samples but not adequate on 17-March for 15 ppm samples. Stability of the test chemical in the diets and the variation between the target and actual concentrations in the diets was acceptable.

4. Statistics: Males and females were analyzed separately for all measures. Adjusted mean bodyweights were determined by correcting for intergroup differences in mean initial bodyweight. These adjusted means were calculated statistically using ANCOVA. Weekly food consumption and food utilization during the periods of Weeks 1-4, 5-8, 9-13, and 1-13 were considered by ANOVA. Brain weights were also analyzed by ANOVA and adjusted for body weights via ANCOVA. Differences in food consumption, motor activity, time to tail-flick, foot splay, and grip strength were determined by ANOVA. The post-hoc test used to identify where differences were significant from controls was a two-sided student's t-test. Significance was set at $p<0.05$ or $p<0.01$.

C. METHODS / OBSERVATIONS:

1. Mortality and clinical observations: Cageside observations were recorded daily. Detailed clinical observations, including the finding of "no abnormalities detected" were recorded weekly. FOB was performed during Weeks -1 (pre-test), 1, 4, 8, and 13.

2. Body weight: Animals were weighed during week -1, on Day 1(immediately before feeding the experimental diet commenced) and then on the same day (where practicable) of each subsequent week up until termination, as well as on the day of termination. In Weeks -1 (pre-test), 1, 4, 8, and 13 animals were weighed as part of the FOB.

3. Food consumption: Food residues and the amount of food given were recorded at weekly intervals or more frequently (if required) and food consumption was calculated, at weekly intervals, as a mean value (in g food/rat/day) for each cage. The food utilization value per cage was calculated as the bodyweight gained by the rats in the cage per 100 g of food eaten for weeks 1-4, 5-8, 9-13, and 1-13 (overall).

4. Opthalmoscopy: The eyes from all rats were examined prior to the start of the study. The eyes from control and high dose rats were examined during week 13.

5. Neurobehavioral assessment:

a. Functional observational battery (FOB):
FOB was performed one week prior to dosing (pre-test) and in Weeks 1, 4, 8, and 13 of dosing. The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
	Posture*	X	Reactivity*		Mobility
	Biting	X	Lacrimation* / chromodacryorrhea		Rearing+
	Convulsions*	X	Salivation*	X	Arousal/ general activity level*
	Tremors*	X	Piloerection*	X	Convulsions*
X	Abnormal Movements*	X	Fur appearance	X	Tremors*
	Palpebral closure*		Palpebral closure*	X	Abnormal movements*
	Faeces consistency	X	Respiratory rate+	X	Urination / defecation*
X	Vocalization	X	Red/crusty deposits*	X	Grooming (appearance)
	SENSORY OBSERVATIONS	X	Mucous membranes /eye /skin color	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*		Gait score*
X	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behavior*
X	Startle response*	X	Convulsions		Backing
X	Pain response*	X	Vocalization		Time to first step
X	Pupil response*	X	Tremors	X	Vocalization
X	Eyeblink response	X	Ptosis	X	Ataxia
	Forelimb extension	X	Thin appearance/sides pinched in	X	Reduced limb (hind, fore) function
	Hindlimb extension	X	Dehydration	X	Reduced stability
X	Air righting reflex+	X	Urination/defecation	X	Curvature of spine
	Olfactory orientation		**PHYSIOLOGICAL OBSERVATIONS**	X	Piloerection
X	Visual placing response	X	Body weight*	X	Sides pinched in
X	Pinna reflex	X	Body temperature+		**NEUROMUSCULAR OBSERVATIONS**
					Hindlimb extensor strength
			OTHER OBSERVATIONS	X	Forelimb grip strength*
		X	Vocalization during removal from cage	X	Hindlimb grip strength*
		X	Time to tail flick	X	Landing foot splay*
					Rotarod performance
				X	Splay reflex

b. **Locomotor activity:** Locomotor activity was evaluated one week prior to dosing (pre-test) and in Weeks 1, 4, 8, and 13 of dosing. Locomotor activity was monitored on an automated activity recording apparatus (Colburn Lab Linc Intra-red Motion Activity System), which records small and large movements as an activity count. Measurements were made on individual animals. Each observation period was divided into 10 scans of 5 minutes in duration in which the animals did not have access to food, water, or items of environmental enrichment. Treatment groups were counter-balanced across test times and devices. Motor activity was assessed in a separate room to avoid disturbances.

6. **Sacrifice and pathology:** At terminal sacrifice, 5/sex/dose were anaesthetized and killed by perfusion-fixation with formal saline for neruopathological analysis. The remaining 5/sex/dose were killed by overexposure to halothane and discarded. Tissues taken after perfusion-fixation are summarized below. All tissues from control and high dose group animals were processed for histopathology. Transverse and longitudinal sections of proximal sciatic nerve, proximal tibial nerve, and distal tibial nerve (tibial nerve calf muscle branched) were embedded in resin and

semi-thin sections were cut and stained with toluidine blue. All other tissue, including longitudinal sections of spinal cord (at cervical and lumbar swellings) were trimmed and embedded in paraffin wax. Five micron sections were cut and sections were stained with haematoxylin and eosin.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	7 Transverse sections (not specified)		Mid-thigh
	Forebrain		Sciatic Notch
	Center of cerebrum	X	Proximal sciatic nerve*
	Midbrain		
	Cerebellum		**OTHER**
	Pons		Sural Nerve
	Medulla oblongata	X	Tibial Nerve (proximal and distal)*
	SPINAL CORD		Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling	X	Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
	Gasserian Ganglion	X	Cervical dorsal root fibers
	Trigeminal nerves	X	Cervical ventral root fibers
X	Optic nerve*		
X	Eyes (with retina)*		
X	Gastrocnemius muscle*		

7. **Positive controls:** Positive control studies conducted during 2003-2004 have been reviewed previously. It was concluded from these studies that Central Toxicology Laboratory, UK has demonstrated proficiency in testing for learning and memory with the Y-maze (MRID 46012924), motor activity in pups (MRID 46336201) and adults (MRID 46336203), FOB in adults (MRID 46336203), grip strength in adults (MRID 46336202), and neuropathology and brain morphometry in pups (MRID 46332604) and adults (MRID 46336203).

Additional references listed in the report included MRIDs 43013301, 43013302, 43013304, 43013303, 45811001, 45811002, 45811003, 46012923, and 43013305. These studies were conducted during 1990-2000; it is not known whether they have been reviewed by EPA.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs:** There were no treatment-related clinical signs observed during the study.

2. **Mortality:** One15 ppm male was found dead on Day 22 (examined at 9:12 h and observed to be normal but found dead a 09:44 h). *Post mortem* revealed a dark, partially inflated lung, clear fluid exuding from the nasal passages, and unilateral pelvic dilation of the kidney. This death was considered by the reviewers an effect of treatment (even though it occurred in a low-dose

group in only one animal) because the effects are consistent with the known toxic effects of paraquat dication on the lungs and kidneys.

B. BODY WEIGHT AND BODY WEIGHT GAIN:

There were no effects of the test chemical on mean body weights at any time. Adjusted mean bodyweight was statistically ($p<0.05$) reduced (↓1.3%) compared to controls for males only during Week 2 at 150 ppm. This small reduction in adjusted mean bodyweight correlated with a small reduction in food consumption during Week 1 in these animals, which was attributed to palatability. This effect was not considered adverse and was also transient, since bodyweights in these animals recovered by Week 3 and were similar to controls for the duration of the study.

C. FOOD CONSUMPTION:

A small reduction in food consumption during Week 1 was observed in 150 ppm-treated males. This reduction in food consumption was transient (attributed to palatability) and did not adversely impact bodyweights and so was not considered adverse.

D. OPTHALMOSCOPY

The eyes for control and high-dose rats prior to the start of the study and during Week 13 (prior to termination) were normal. While on study, one 15 ppm animal developed hazy corneal opacity and stained eyelids in the left eye and one 50 ppm animal developed a persistent papillary membrane in the left eye. Since these effects were dissimilar, occurred only in one animal in the lower dose groups, and were not observed in high-dose animals, they were not considered treatment-related.

E. NEUROBEHAVIORAL RESULTS:

1. FOB findings:

There were no effects of the test substance on FOB parameters. Statistically significant differences in some FOB parameters were identified that were not considered an effect of the test substance. These parameters and rationale are summarized below:

- Foot splay reflex: Incidences of reduced foot splay reflex were noted across all dose groups in males and females. However, the severity and number of animals affected were comparable between controls and treatment groups and so this was not considered an effect of the test chemical.
- Landing foot splay: A small, statistically significant difference in landing foot splay was noted in 50 ppm males at Week 13 only. This was also not considered an effect of the test chemical because this effect occurred only in one sex, at one dose, and at one time point.
- Time to tail-flick: The time to tail flick was statistically different for 50 ppm males and females during Week 1 after dosing. Since this was observed only at Week 1 and only in the mid-dose group, it was not considered treatment-related.
- Hindlimb grip strength: Statistically significant differences in hindlimb grip strength were observed in 15 ppm females (compared to controls) during Week 13 after dosing. This effect occurred only in one sex, at one time point, and only in the low dose group. Therefore, it was not considered treatment-related.

2. Motor activity: There were no effects of the test chemical on total motor activity and no consistent or dose-dependent effects of the test chemical on subsession motor activity. Overall motor activity was statistically different compared to controls during Week 13 after dosing only in males. Subsessions within all sessions showed habituation. Subsession motor activity was statistically different compared to controls during Week 1 after dosing in females at 15 ppm (41-45 minutes), during Week 13 in males at 15 ppm (6-10 minutes, 20-26 minutes), 50 ppm (6-10 minutes), and 150 ppm (26-30 minutes) and in females at 50 ppm (1-5 minutes). However, these differences in subsession motor activity were not consistent across dose, sex, or time and so were not considered treatment related. Overall motor activity and selected subsession motor activity are summarized in Table 8.

TABLE 8. Motor activity (total activity counts for session or subsession)				
Test day	Dose level (ppm)			
	Control	15	50	150
Males				
Pre-test	303.3±100.1	339.6±118.8	310.4±115.1	318.8±104.8
Week 1	444.3±143.0	473.9±108.3	492.1±132.0	418.1±166.7
Week 4	444.0±98.9	406.6±115.5	477.2±118.6	432.4±164.7
Week 8	383.5±89.2	362.4±145.6	402.6±122.9	421.7±134.5
Week 13	419.6±103.6	328.6±119.9* (↓22%)[a]	387.2±126.0	342.6±110.1
Week 13, Subsession 1-5 minutes	62.1±10.3	65.8±8.2	66.2±7.6	65.3±10.5
Week 13, Subsession 6-10 minutes	73.3±8.8	62.7±15.2* (↓14%)[a]	62.8±9.6* (↓14%)[a]	66.3±11.2
Week 13, Subsession 26-30 minutes	47.8±24.4	21.5±20** (↓55%)[a]	36.5±30.8	16.1±22.2** (↓66%)[a]
Females				
Pre-test	375.3±132.3	382.2±144.8	376.3±138.0	339.6±124.0
Week 1	465.2±140.8	542.8±119.0	510.3±95.0	502.8±68.3
Week 4	511.5±95.3	473.8±161.9	499.9±143.9	497.5±117.2
Week 8	429.1±164.6	463.5±145.2	430.5±189.9	454.4±155.2
Week 13	523.3±157.7	476.9±164.5	508.3±209.7	506.3±147.6
Week 13, Subsession 1-5 minutes	52.3±9.3	52.1±11.7	61.3±8.7* (↑17%)[a]	51.3±13.2

Data were extracted from pages 91-100 of the study report.
Values represent mean counts ±s.d.
n=12/sex/dose
[a]Calculated by reviewers
*=p<.05,** p<.01 compared with controls

F. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** There were no treatment-related gross pathological findings in any animal that survived to scheduled sacrifice.

2. **Brain weight:** There were no effects of the test substance on absolute brain weights, or on brain weights relative to body weights.

3. **Neuropathology:**

There were no treatment-related microscopic findings. Incidences of demyelination/nerve fiber degeneration (a common spontaneous finding) were noted in both control and high dose group animals. These lesions were of similar incidence and severity in treated and control animals and so were not considered test article-related.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS CONCLUSIONS:

A comprehensive battery of neurobehavioral tests and neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of up to 150 ppm paraquat cation.

The NOAEL was 150 ppm (equivalent to 10.2-11.9 mg paraquat cation/kg in males/females). The LOAEL was not observed.

B. REVIEWER COMMENTS:

Mortality was observed in one 15 ppm male. Otherwise, there were no clinical signs associated with the test material. No effects of the test material were observed in the functional observational battery. There were also no effects of the test material on motor activity. There were also no effects of the test material on brain weights and there were no neuropathological findings.

Dosing was considered adequate, based on a previous, acceptable three-generation reproduction toxicity study in this species and strain (MRID 00126783) in which technical grade paraquat dichloride (32.7% w/v paraquat cation) was administered continuously in the diet to Wistar-derived Alderley Park rats (15 males and 30 females/dose) at dose levels of 0, 25, 75, or 150 ppm (approximately equivalent to 0, 1.25, 3.75, and 7.5 mg paraquat ion/kg/day, assuming that for an older rat, 1 ppm = 0.05 mg/kg/day). Parents were fed test diets for 11-12 weeks before they were mated to produce the F1, F2, and F3 litters. High mortality was observed in the 150 ppm P, F1, and F2 females (17-43%) compared to controls (0-4%). These deaths were considered to be due to severe lung damage caused by paraquat. The incidence of lung lesions (red or purple discoloration, congestion, edema, fibrosis, hyaline membrane formation, inflammatory cell infiltration, and/or hyperplasia) ranged from 27-35% in these animals compared to 0 controls. There were no effects of treatment on clinical signs, body weights, body weight gains, food consumption, food utilization, ophthalmology, hematology, clinical chemistry, or urinalysis.

One15 ppm male was found dead on Day 22 (examined at 9:12 h and observed to be normal but found dead a 09:44 h). *Post mortem* revealed a dark, partially inflated lung, clear fluid exuding from the nasal passages, and unilateral pelvic dilation of the kidney. The Study Director considered this death unrelated to the test substance because it occurred in a low-dose group in one animal with no apparent cause of death. EPA reviewers disagree, and consider this death test substance related because it is consistent with what is known about the mechanisms of paraquat toxicity.

The mechanism of paraquat-induced toxicity (with the exception of neurotoxicity) is well characterized. Paraquat is rapidly absorbed from the small intestine and delivered to multiple organ systems (e.g. liver, heart, kidneys, lungs) where it undergoes redox cycling, causing tissue damage. The kidneys are a major route of elimination of paraquat and so receive high exposure and damage from paraquat cation. However, the lungs are the most susceptible organ system for two reasons. First, there is increased accumulation in the lungs compared to other tissues (due to active transport of paraquat dication). Second, the lungs repair tissue damage from paraquat

dication via a fibrotic (scaring) response. This scaring can reduce lung elasticity, which can result in dyspnea, cyanosis, and respiratory failure[1]. The observed death in this animal shows evidence of a collapsed lung (partially inflated with fluid exudating from the nasal passages), which is consistent with sudden respiratory failure. The dilation of the renal pelvis may indicate damage to the kidney via paraquat dication.

The NOAEL for subchronic neurotoxicity was 150 ppm (equivalent to 10.2-11.9 mg paraquat cation/kg in males/females). The LOAEL was not observed.

C. STUDY DEFICIENCIES:

The 15 ppm diet prepared on 17-March was not homogenous (variability above 10%). This is not considered to impact the scientific interpretation of the study because homogeneity was acceptable for the 150 ppm diets on all analysis dates, and 150 ppm was the NOAEL for neurotoxicity.

[1] Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat Poisonings: Mechanisms of Lung Toxicity, Clinical Features, and Treatment. *Critical Reviews in Toxicology,* 38:13–71, 2008

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R182282

Chemical Name: Paraquat dichloride
Paraquat

PC Code: 061601

061603

HED File Code: 13000 Tox Reviews
Memo Date: 5/11/2010
File ID: 00000000
Accession #: 000-00-0135

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5/19/2010